REMARKS

Amendments

In item 2 of the Office Action, the Examiner asks that the recitation of "a parasitic infection, interstitial cystitis and asthma" be removed from claim 37 in view of the restriction dated June 4, 2001 and subsequent election dated August 7, 2001. Applicants have followed the Examiner's request (hence the cancellation of claim 40 as moot), but note for the record that the amendment does not relate to patentability and, moreover, Applicants point out that the cancelled indications, including asthma, are examples of IgE-mediated allergic diseases (see, *e.g.*, line 22 on page 2 of the Office Action, "allergy therapy (i.e., IgE-mediated disease)"...) and hence encompassed as species within genus claim 37.

Claims 46-49 have been added which find specification or prior claim basis at least as follows:
claim 46 - page 22, line 29
claim 47 - claim 38
claim 48 - claim 39
claim 49 - claims 45, 38, 39 and page 22, line 29.

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

Substitute Declaration

Applicants are submitting by hand carry under separate cover an executed second substitute declaration. The substitute declaration filed April 19, 2002 was inadvertently co-signed by inventors Cleland, Lam, Overcashier and Yang who were actually previously removed as inventors by way of 1.48(b) Petition filed November 2, 2000. The second substitute declaration excludes the signatures of these cancelled inventors. Entry of this second, substitute declaration into the case, to replace the previously submitted declarations, is respectfully requested.

IDSs

Applicants note with respect to item 6 of the Office Action only an initialed copy of page 2 of the PTO-1449 was attached to the latest Office Action. Thus, the following PTO-1449 numbered references have not yet been indicated to be considered - ref. nos. 80-82, 85-86, 88-95, 98, 101-106, 118-120, 122-142, 144, 147-160, 162-171, 173-177, 181, 183-203, 205-208 and 209-290.

Applicants are hand delivering under separate cover, for the third time, the missing references and clean PTO-1449 forms, so that all references cited can be indicated to have been considered. Consideration of the art and return of all the initialed PTO-1449 forms is respectfully requested.

Section 103

Claims 37-40, 44 and 45 are rejected under 35 USC Section 103 as being unpatentable over US Patent No. 5,965,709 ("the '709 patent") in view of US Patent No. 4,093,606 ("the '606 patent").

The '709 patent is said to disclose allergy therapy (IgE-mediated disease) by administration of an anti-IgE antibody or anti-IgE fragment such as Fab or Fab', including by subcutaneous injection, in amounts of about 2-3mg/kg, as well as pharmaceutical excipients which would serve as lyoprotectants. The Examiner acknowledges that the '709 patent does not teach anti-IgE antibody in an amount of about 50mg/mL to about 400mg/mL.

The '606 patent is said to disclose a reconstituted formulation of antibody for use in treating infection in a mammal, including humans, comprising glycine, albumin and a non-ionic surfactant, where the antibody is in an amount of 50mg/mL, and further that the preparation can be prepared by reconstitution of lyophilized antibody in sterile water.

The Examiner urges that it would have been *prima facie* obvious to have reconsituted the anti-IgE antibody in the pharmaceutical composition disclosed by the '709 patent at the concentration disclosed for the antibody of the medicinal composition disclosed by the '606 patent for use in the method of treatment disclosed by the '709 patent. The Examiner argues that one would have been motivated to do this because the '709 patent discloses methods of treatment of human disease using a pharmaceutical composition comprising a reconstituted lyophilized antibody and lyoprotectant, and the '606 patent discloses a concentration of 50mg/mL for the reconstituted antibody for use in humans.

Applicants submit that the presently claimed invention is patentable over the cited references.

The '709 patent describes therapy with and pharmaceutical compositions of IgE antagonists including "IgE variants, IgE peptide antagonists, peptidomimetics

and other small molecules" (column 5, lines 15-17). The IgE antagonists can be used in screening antibodies specific to the $Fc_{\epsilon}RI$-binding domain of IgE (column 32, lines 30-43). As acknowledged by the office, the '709 patent does not specifically describe an IgE antibody concentration in a formulation in the range from 50 mg/mL to about 400 mg/mL.

The '606 patent is concerned with a "gamma globulin preparation suitable for administration by intravenous injection and to processes for the preparation of said gamma globulin" (Emphasis added, '606 patent, column 1, lines 13-16). Subcutaneous administration is not taught. If anything, the '606 patent teaches away from anything other than intravenous administration (column 1, lines 45-60 of the '606 patent, for instance.) There is nothing in the '606 patent to suggest that the process therein is applicable to anything other than gamma globulin preparations. Lines 21-33 in column 1 refers to prophylaxis and therapy of infections in patients using gamma globulin preparations. Therapy of IgE-mediated allergic disease is not disclosed or alluded to in the '606 patent. The process in the '606 patent concerns PEG-precipitation of Fraction II or Fraction II and III plasma proteins, followed by dissolving the precipitate in albumin, TWEEN™, and glycine, and adjusting the solution to contain 5 grams of IgG per 100 mL of solution either by dilution or by the addition of more PEG-precipitate. There is nothing in the '606 patent to indicate the PEG-precipitation method therein is applicable to other proteins, much less an IgE antibody preparation. There is no indication that Fraction II and/or III contain IgE antibody, nor that an IgE antibody formulation of the claims herein could be prepared by the PEG-precipitation process in the '606 patent.

Applicants respectfully submit that, absent the benefit of hindsight of the present invention, the skilled person at the relevant date would not have been motivated to combine the disclosures of the '709 patent and the '606 patent as the Examiner has. In particular, both the active ingredient and the indication are completely different in these two patents. The active ingredient in the '606 patent is a mixture of gamma globulins which bind a variety of antigens, the indication is treating infection. On the contrary, the present claims concern an antibody that binds IgE, and treatment of IgE-mediated allergic disease. There is no evidence to demonstrate that the skilled practitioner would consider information in relation to therapy of infection with gamma globulins would be relevant to therapy of IgE-mediated allergic disease with an IgE antibody. The '606 patent disclosure is clearly concerned only with

gamma globulin preparations. There is nothing in the document to indicate that it concerns products other than gamma globulins. Moreover, there is nothing in the '606 patent to suggest that the PEG-precipitation method therein is applicable to products other than gamma globulins. Hence, Applicants submit that the skilled person would not have combined the disclosures of the '606 patent and '709 patent, at the relevant date.

Indeed, the Office has taken the position that "methods for treating different diseases which have different pathologies, etiologies, symptoms and prognoses" are "patentably distinct" (Office Action dated June 4, 2001, Paper #4, at page 2, last 3 lines). Thus, Applicants submit that therapy of an IgE-mediated allergic disease is patentably distinct from therapy of infection as in the '606 patent, and that information concerning a formulation of gamma globulin that might be used to treat infection as described in the '606 patent would not be combined with a teaching concerning therapy of an IgE-mediated allergic disease as in the present claims.

In addition, Applicants submit that the art fails to teach that a formulation comprising an IgE antibody in an amount from 50 mg/mL to about 400mg/mL is desirable, much less that such a formulation is especially adapted for subcutaneous administration (present specification, page 2, lines 16-18). Even if the prior art had taught the desirability of a formulation comprising an IgE antibody in an amount from 50 mg/mL to about 400mg/mL - which is denied - Applicants submit that the art failed to disclose or suggest how to prepare such a preparation, nor did it teach whether or not such a preparation would be stable. Such teachings can be found in the present application in Example 2 on pages 37-43 for instance. Applicants submit that, in the absence of the teachings of the present application, the skilled person would not have had a reasonable expectation of success in generating an IgE antibody formulation as claimed herein which is stable and suitable for therapy, in spite of the very high concentration of the IgE antibody in the formulation.

As to claims 38, 47 and 49 herein reciting subcutaneous administration, Applicants point out that those claims are independently patentable over the art. In particular, the '606 patent is specifically concerned with a formulation (of gamma globulin) for intravenous administration and teaches away from subcutaneous administration. There is no suggestion in the art to administer subcutaneously a composition comprising protein at a concentration from 50 mg/mL to about 400 mg/mL, let alone 80 mg/mL to about 300mg/mL as in

claim 49, to a human.

Turning now to claims 46 and 49, where the antibody concentration is in the range from 80 mg/mL to about 300 mg/mL, Applicants submit that those claims are also independently patentable over the cited art, which failed to disclose or suggest such antibody concentrations.

Hence, Applicants submit that the methods claimed herein are patentable over the cited art. Reconsideration and withdrawal of the rejection in view of the above remarks is respectfully requested.

Respectfully submitted,
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